Clinical Case Report

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Dermatomyositis as an extrahepatic manifestation of hepatitis B virus-related hepatocellular carcinoma

A case report and literature review

Juqiang Han, PhD[a,*], Shuai Wang, PhD[a], Thomas Ngai Yeung Kwong, PhD[b], Jian Liu, PhD[c]

Abstract

Rationale: Dermatomyositis is an idiopathic inflammatory myopathy with specific cutaneous manifestations, which is closely associated with malignancy. However, the exact mechanism remains elusive. Even less is known about dermatomyositis with hepatocellular carcinoma (HCC).

Patient concerns: We reported a case of dermatomyositis with hepatitis B virus (HBV) infection. He incidentally found his lower limbs little weakness accompanied with his wrist erythema. He was found HBsAg positive for forty years with slightly positive of α-fetal protein (AFP).

Diagnoses: A dermapathology from his hand-wrist lesions demonstrated a scattered inflammatory infiltrate around the capillaries of the dermis. Abdominal enhanced computer tomography (CT) revealed infiltrative HCC affecting the whole liver, accompanied by liver metastasis and liver cirrhosis. Liver tumor needle biopsy pathology showed HCC with moderate differentiation. The left supraclavicular lymph node needle biopsy pathology confirmed metastasic HCC.

Interventions: Prednisolone was gradually withdrawn with the introduction of Entecavir 0.5 mg daily. Radiofrequency ablation therapy for liver tumor was performed once in order to decrease the tumor load.

Outcomes: His muscle power improved to grade 4+/5 in the lower limb one month after anti-HBV treatment. However, this patient died finally from liver failure due to the development of liver tumor.

Lessons: In the coming clinic work, we must pay more attention to the extrahepatic disorder induced by HBV. On treating experience, glucocorticoid administration is often contraindicated for HBV infected patients because of its potential promotion of HBV replication. Thus, it is necessary to administrate high-effective anti-HBV drug prior to glucocorticoid treatment in order to prevent liver failure.

Abbreviations: ALT = alanine amino-transferase, AST = aspartate amino-transferase, CK = creatine kinase, CT = computer tomography, DM = dermatomyositis, EMG = electromyogram, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, HTLV-1 = human T leukemia/lymphoma virus type I, LDH = lactate dehydrogenase.

Keywords: dermatomyositis, extrahepatic manifestation, hepatitis B virus, hepatocellular carcinoma, paraneoplastic syndrome

1. Introduction

Dermatomyositis is an idiopathic inflammatory myopathy with specific cutaneous manifestations likely due to autoimmune reaction. Although the exact pathogenesis remains uncertain,[1] dermatomyositis is typically considered as paraneoplastic syndrome because of its close association with malignant tumors.[2] Hepatocellular carcinoma (HCC), with high morbidity and mortality, represents one of the most common human malignancies in Asia and Africa. However, the relationship between dermatomyositis (or polymyositis) and HCC is under investigated. Hepatitis B virus (HBV) is a major risk factor of HCC development. Occasionally, HBV infection is reported to cause a variety of extrahepatic manifestations, including polymyositis and dermatitis,[3–6] but the specific mechanism remains elusive. Herein, we report in this paper a rare case of dermatomyositis with HBV-related HCC.

2. Case report

A 62-year old male was HBsAg positive for 40 years, but he had never felt any uncomfortable symptoms. Until February 9, 2015, he incidentally found his lower limbs little weakness accompanied with his wrist erythema as well as slightly positive of α-fetal protein (AFP), he did not take care of it yet. In March 10, 2015, he gradually felt the difficulty in walking on feet. Electromyogram (EMG) examination showed muscle damage in bilateral deltoid,

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JH and SW contributed equally to this work.

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[a] Institute of Hepatology, PLA Army General Hospital, Beijing, PR China, [b] Department of Medicine and Therapeutic, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, [c] Department of Rheumatology, Aerospace Center Hospital, Beijing, PR China.

[*] Correspondence: Juqiang Han, Institute of Hepatology, PLA Army General Hospital, Nanmencang 5, Dongcheng District, Beijing 100700, China (e-mail: hanjuqiang2014@126.com).

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bilateral quadriceps and left musculus biceps brachii. Therefore, he was diagnosed as dermatomyositis and treated with the large amount of glucocorticoids (32 mg/d/oral) for 3 months. Unfortunately, his symptoms of muscle power weakness improved little significantly, and the serum levels of creatine kinase (CK) still stayed at higher lever of 615 IU/L. In June 2, 2015, the patient felt incidentally his left supraclavicular lymph nodes enlarged. Further investigation such as the abdominal computer tomography (CT) and PET-CT showed liver neoplasm with intrahepatic metastasis. However, this patient rejected the further treatment on HCC. About 1 week later, the patient began to feel difficulty in standing up accompanied with persist anorexia. So, he was referred to our department of liver disease in June 10, 2015.

The patient had no history of blood transfusion, tattooing, or intravenous drug addiction except family history of HBV infection. Physical examination revealed typically red edematous erythema around his eyes, extinctive heliotrope rash over his wrists, poikiloderma on the back neck (Fig. 1), and bilateral edema on dorsum of feet. Musculoskeletal examination showed muscle power about grade 2 in the symmetrically proximal muscles of both lower extremities. In addition, several tumescent lymph nodes were touched up his left supraclavicular region.

Further investigations showed elevated serum levels of creatine kinase (CK) (741 IU/L) and lactate dehydrogenase (LDH) (405 IU/L), but the liver function tests were normal. ESR was also normal at 10 mm/h. All autoantibodies, other than antinuclear antibody of 1:640, including anti-SMA, anti-ENA, anti-RHF, antidouble-stranded DNA, anti-RNP, anti-Sm, anti-SSA, anti-SSB, anti-Scl 70, anti-Jo-1, anti-Hu, anti-Yo, anti-Rui, anti-P155/140 and anti-Mi2, were negative. All tumor biomarkers in serum, including CEA (carcinoembryonic antigen), PSA (prostate-specific antigen), NSE (neuron-specific enolase), CA125 and CA72-4 (glucoprotein antigen), were normal except AFP of 36.43 ng/mL and CA19-9 of 222.8 u/L. EMG examination indicated that there were severe injuries in his bilateral deltoid muscle, quadriceps femoris and left biceps brachii. However, biopsy from aforementioned muscles showed no abnormality. On the contrary, derma pathology from his hand-wrist lesions demonstrated a scattered inflammatory infiltrate around the capillaries of the dermis (Fig. 2). Abdominal-enhanced computer tomography (CT) revealed infiltrative HCC affecting the whole liver, accompanied by liver metastasis and liver cirrhosis. Liver tumor needle biopsy pathology showed HCC with moderate differentiation. The left supraclavicular lymph node needle biopsy pathology confirmed metastasic HCC (Fig. 3). The patient had positive hepatitis B surface antigen, antihepatitis B e antibody and total antihepatitis B core antibody. The serum HBV DNA level was 9.2×10^7 copies/mL. Additionally, all types of antibodies from viral infection including human immunodeficiency virus (HIV), coxsackie virus, adenovirus, influenza virus, human T-cell leukemia/lymphoma virus type I (HTLV-1) and rubella virus were negative.

Due to active HBV replication, prednisolone was gradually withdrawn with the introduction of entecavir 0.5 mg daily, a specific antiviral drug for inhibiting HBV replication. HBV DNA became undetectable a week later. Unexpectedly, his muscle power improved to grade 4+/5 in the lower limb 1 month after anti-HBV treatment. His CK level also gradually returned to normal (Fig. 4), while the α-fetoprotein was maintained at a slightly high level on follow-up at the clinic. With the development of liver tumor, this patient died finally from liver failure in May 14, 2016, and his attendants refused autopsy.

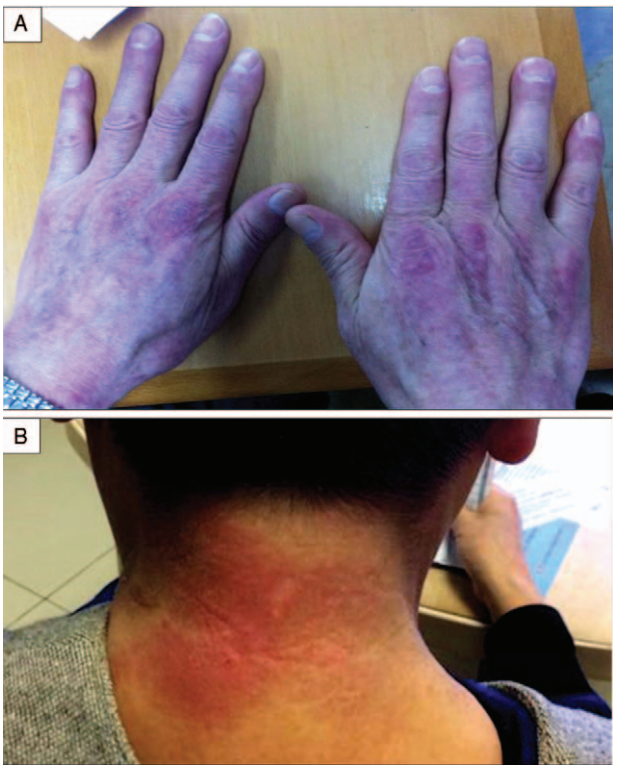

Figure 1. Clinical manifestation of dermatomyositis in this patient. (A) Extinctive heliotrope rash over his wrists. (B) Poikiloderma on the back neck.

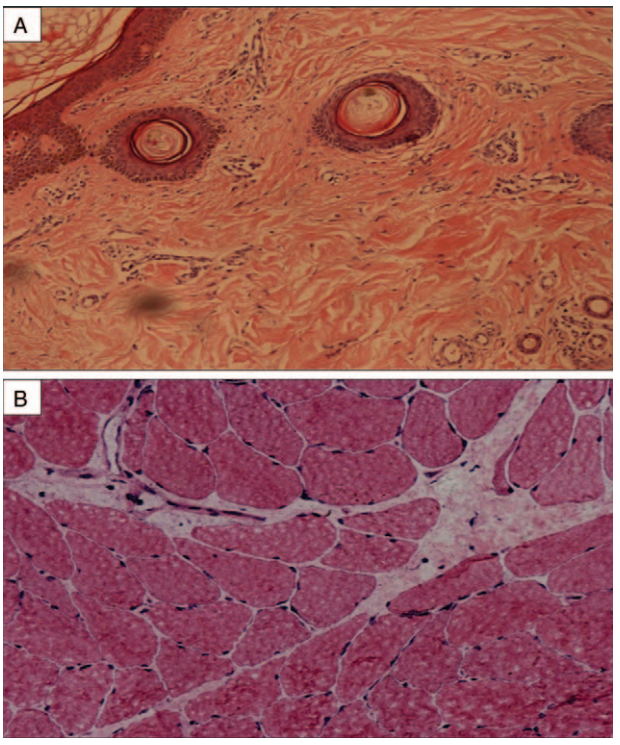

Figure 2. Both dermis and muscle tissues armed with HE staining (×200). (A) Showed a scattered inflammatory infiltrate around the capillaries of the dermis on hand wrist. (B) Indicated no abnormal symbol in the quadriceps femoris muscle.

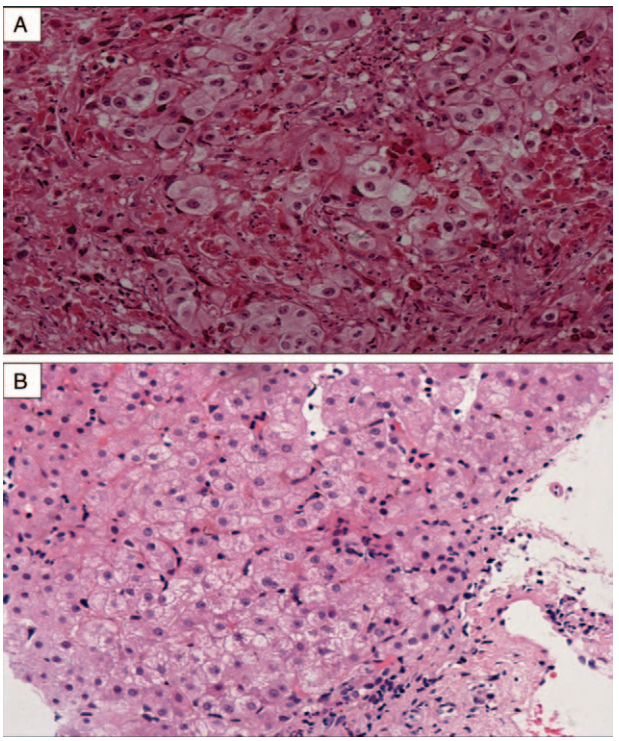

Figure 3. Both lymph node and liver tumor tissues armed with HE staining (×200) as well as radiological findings of HCC. (A) Revealed HCC metastasis in the left supraclavicular lymph nodes. (B) Showed HCC in liver. HCC = hepatocellular carcinoma.

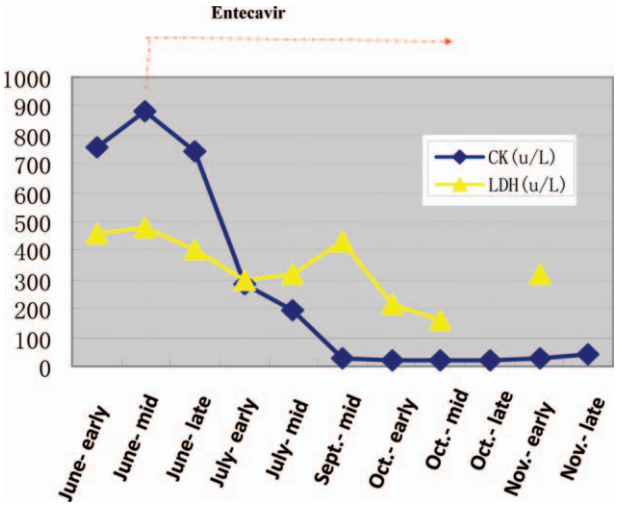

Figure 4. CK spectrum post-medical treatment of anti-HBV treatment. CK = creatine kinase, LDH = lactate dehydrogenase.

3. Discussion

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases and are not directly related to the physical effects of the primary or metastasis tumors. Current understanding of the interplay between paraneoplastic syndromes and cancer arise from secretion of functional peptides or hormones from the tumor, or inappropriate immune cross-reactions against normal host cells, which are intended to target the tumor cells. Generally, there is no correlation between the severity of clinical symptoms and the size of the primary tumor, and in some cases, paraneoplastic syndromes may manifest before the diagnosis of cancer.[7] Clinically, about 6 to 60% of cases of malignant tumor are found to be associated closely with dermatomyositis,[8,9] which is often considered as the typical paraneoplastic syndrome. Regarding to myositis-specific anti-p155/140 antibodies have been identified in 50% of cancer-associated myositis cases, significantly higher than in noncancer-associated myositis (4.1%).[10] In addition, positive anti-Hu/Yo/Rui antibodies are one of the important phenotypes in diagnosing neurologically paraneoplastic syndrome. However, the association between dermatomyositis and malignancy is not consistently shown in all studies. Voravud et al[11] demonstrated that no difference has been found between the idiopathic presentation of dernatomyositis and that associated with malignancy. The development of HCC is often associated with paraneoplastic syndrome, including hypercholesterolemia, hypoglycemia, erythrocytosis, and hypercalcemia, other rare associations include porphyria cutaneatarda, virilization and feminization syndrome, carcinoid syndrome, hypertrophic osteoarthropathy, hyperthyroidism, and osteoporosis. Dermatomyositis is among one of the rarest. In this present case, dermatomyositis had already occurred for 4 months prior to the diagnosis of HCC by CT and PET-CT, which is consistent with the criteria for the diagnosis of paraneoplastic syndrome. However, those aforementioned antibodies were not detected in this case. The binding of antibodies to Mi-2, which is a component of the nucleosome remodeling-deacetylase complex, is strongly associated with dermatomyositis (and/or polymyositis) because of their cross-reactivity with HCC.[12] Yet, anti-Mi-2 antibodies were not detected positive in this patient. Therefore, the fact that all the specific antibodies were not detected from this patient indicated dermatomyositis might be correlated with other diseases, independent from HCC.

Major risk factors associated with pathogenesis of HCC include HBV or hepatitis C virus (HCV) infection, alcoholic liver injury, high-cholesterol-induced hepatic steatosis and intake of aflatoxins. We searched on PubMed website (http://www.ncbi.nlm.nih.gov/pubmed) using the terms "liver neoplasm" and "paraneoplastic syndrome" and identified 10 cases (see Table 1)[13–19] that showed dermatomyositis did not co-exist with other causative-agents-induced HCC except for HBV or/and HCV. This indicates the close correlation between hepatitis virus and paraneoplastic syndrome. In fact, HCV infection alone has been demonstrated to associate with the presence of autoantibodies and various types of autoimmune diseases such as dermatomyositis (see Table 2).[20–26] For this reason, we populate that the induction of dermatomyositis is linked to HCV infection rather than HCC. Similarly, HBV infection is occasionally reported to result in a spectrum of extrahepatic disorders including dermatomyositis, polyarthralgias and arthritis, glomerulonephritis, polymyositis, aplastic anemia, neuropathy, and vasculitis.[3] Subsequently, we identified 2 papers demonstrating the use of HBV-vaccine-induced dermatomyositis by searching with the terms "hepatitis B virus" and "dermatomyositis" on PubMed. To date, although the mechanism of action remains to be fully elucidated, a number of hypotheses have been described about the pathogenesis of HBV-related extrahepatic disorders, including the deposition of circulating HBV antigen–antibody complexes in extrahepatic tissues,[27] the local induction of immune complex formation in extrahepatic tissues, viral induction of host autoantibodies reactive with extrahepatic tissues,[28] and possible extrahe-

Table 1

Etiological comparison among 10 cases of dermatomyositis with hepatocellular carcinoma through literature review.

Authors	Published year	Viral infection	Age	Gender	Pathological biopsy
Gray et al[13]	1976	Not done	36	Male	HCC
Horie et al[14]	1989	Not done	56	Female	Combined HCC–CCC
Inuzuka et al[15]	2001	HCV	51	Male	HCC
Kee et al[5]	2004	HCV	71	Male	HCC
Toshikuni et al [16]	2006	HCV	79	Female	HCC
Gomez et al[17]	1997	HCV	73	Male	HCC
Kee et al[1]	2009	HBV	58	Male	HCC
Cheng et al[18]	2002	HBV	50	Female	HCC
Yang et al[19]	2014	HBV	55	Male	HCC
This present case		HBV	62	Male	HCC

HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus.

Table 2

Hepatitis viral component solely induced dermatomyositis among 11 cases through literature review.

Authors	Published year	Age	Gender	Etiological agent
Nishikai et al[20]	1994	48	Male	Not done
Fiore et al[21]	1996	72	Male	HCV
Fiore et al[21]	1996	70	Male	HCV
Fiore et al[21]	1996	65	Male	HCV
Moccia[22]	1998	65	Female	HCV
Nakamura et al[23]	2000	60	Female	HCV
Germany et al[24]	2002	40	Female	HCV
Fiore et al[21]	1996	—	Female	HCV and HBV
Fiore et al[21]	1996	68	Male	HCV and HBV
Altman et al[25]	2008	6	Female	HBV vaccine
Fernandez-Funez et al[26]	1998	13	Male	HBV vaccine

HBV = hepatitis B virus, HCV = hepatitis C virus.

patic viral replication.[29] Interestingly, Mason et al[30] presented an important evidence of active HBV replication in the vascular endothelium of a patient with polymyositis, which directly mirrors a milestone of the tissue distribution affected by HBV-related extrahepatic disease. In the present case, we were unable to detect positive HBsAg or HBcAg in the extrahepatic tissues. However, muscle strength was significantly improved once we administrated the antiviral treatment. Clinically, prednisolone shock therapy is the preferred treatment strategy in the early stage dermatomyositis. In the present study, however, the administration of prednisolone did not improve the patient's weak muscle strength during early stage of treatment. For this reason, we firmly believe that dermatomyositis is a type of extrahepatic disorder that is induced by HBV infection in this patient instead of liver-tumor-induced paraneoplastic syndrome.

In this study, we highlighted the potential association between dermatomyositis and HBV. In the coming clinic work, we must pay more attention to the extrahepatic disorder induced by HBV. On treating experience, glucocorticoid administration is often contraindicated for HBV infected patients because of its potential promotion of HBV replication. Thus, it is necessary to administrate high-effective anti-HBV drug prior to glucocorticoid treatment in order to prevent liver failure.

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Author contributions

Conceptualization: Juqiang Han.
Data curation: Juqiang Han, Shuai Wang, Jian Liu.
Formal analysis: Juqiang Han, Thomas Ngai Yeung Kwong.
Investigation: Juqiang Han, Shuai Wang.
Methodology: Juqiang Han.
Project administration: Juqiang Han.
Resources: Juqiang Han, Shuai Wang, Jian Liu.
Software: Juqiang Han.
Supervision: Juqiang Han.
Validation: Juqiang Han.
Visualization: Juqiang Han.
Writing – original draft: Juqiang Han.
Writing – review & editing: Juqiang Han, Thomas Ngai Yeung Kwong.

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